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16. ABSTRACT

Because minimal data are available regarding the pulmonary effects of ozone (O_3) at levels <0.27 ppm, six groups of healthy young males were exposed for 2.5 h to one of the following O_3 concentrations: 0.0, 0.12, 0.18, 0.24, 0.30, or 0.40 ppm. Fifteen-minute periods of rest and exercise (65 1/min minute ventilation) were alternated during the first 2 h of exposure. Coughing was observed at all levels of O_3 exposure. Small changes in forced-expiratory spirometric variables (forced vital capacity (FVC), forced expiratory volume in 1 s, and mean expiratory flow rate between 25 and 75% FVC) were observed at 0.12 and 0.18 ppm O_3, and larger changes were found at O_3 levels ≥ 0.24 ppm. Changes in tidal volume and respiratory frequency during exercise, specific airway resistance, the presence of pain on deep inspiration, and shortness of breath occurred at O_3 levels ≥ 0.24 ppm. In conclusion, pulmonary effects of O_3 were observed at levels much lower than that for which these effects have been previously described. Stimulation of airway receptors is probably the mechanism responsible for the majority of observed changes; however, the existence of a second mechanism of action is postulated.

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Pulmonary effects of ozone exposure during exercise: dose-response characteristics

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air pollution; pulmonary function testing; environmental chamber studies

ACUTE PULMONARY FUNCTION CHANGES in humans after ozone (O_3) exposure have been documented at levels ≥ 0.27 parts per million (ppm) by volume. Attempts to characterize responses below this level, however, have been limited by small numbers of subjects and exposure to few O_3 levels. Consequently dose-response characteristics of the pulmonary effects of O_3 are poorly defined at levels < 0.27 ppm. The available data indicate that the lowest level of O_3 producing pulmonary effects in healthy subjects performing heavy exercise may be between 0.20 and 0.27 ppm. Folinsbee et al. (7) reported decrements in pulmonary function at 0.27 and 0.43 ppm O_3, but not at 0.11 ppm. In that study, O_3 levels were measured by the neutral buffered KI method. Folinsbee et al. (7) estimated that their nominal levels of 0.10, 0.30, and 0.50 are approximately equivalent to 0.11, 0.27, and 0.43 ppm as measured by the ultraviolet method now most commonly used. DeLucia and Adams (5) found significant pulmonary function decrements at 0.3 but not at 0.15 ppm O_3. Adams et al. (1) also reported decrements at 0.3 ppm O_3; however, no changes were noted for pulmonary function during exposure to 0.2 ppm.

The purposes of the present study were to discern the lowest concentration of O_3 at which decrements in pulmonary function occur and to describe the dose-response relationships between low-level O_3 exposure and acute changes in pulmonary function and symptoms. Large numbers of subjects were exposed to one of three concentrations of O_3 < 0.27 ppm with heavy exercise. The results indicate that significant group mean changes in pulmonary function and symptoms did indeed result from such exposure to O_3 levels < 0.27 ppm.

MATERIALS AND METHODS

Healthy male volunteers (n = 135), 18–30 yr of age, served as subjects for this study. Most of these volunteers were college students. Potential subjects were excluded from participation if they had smoked within 3 yr or had a history of asthma, allergic rhinitis, cardiac disease, chronic respiratory disease, recent acute respiratory illness, or extensive exposure to pollutants. All potential subjects underwent screening procedures, including completion of the Minnesota Multiphasic Personality Inventory and a medical history form, physical examination and routine chemical and hematologic screens. Accepted subjects were informed of the purposes, experimental protocol, and procedures of the experiments, as well as potential risk from participation, and each subject signed a statement of informed consent. This study was approved by the Committee on the Protection of the Rights of Human Subjects of the University of North Carolina School of Medicine. Physical characteristics of the subjects are presented in Table 1.

At least 1 day before exposure, subjects were trained in the techniques for obtaining plethysmographic and spirometric measurements. At this time they also exercised on a treadmill, and the speed and grade of incline required to produce a minute ventilation ($\dot{V}_E$) of approximately 35 $l \cdot min^{-1} \cdot m^{-2}$ body surface area (BSA) were

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TABLE 1. *Characteristics of exposure groups*

	Group No.					
	1 (n = 20)	2 (n = 22)	3 (n = 20)	4 (n = 21)	5* (n = 21)	6 (n = 20)
O_3, ppm	0.00	0.12	0.18	0.24	0.30	0.40
	±0.00	±0.00	±0.00	±0.01	±0.01	±0.01
Age, yr	22.5	22.3	23.3	22.9	23.1	22.8
	±3.1	±3.1	±2.8	±2.9	±3.0	±3.5
Ht, cm	180	183	180	175	180	181
	±8.1	±6.0	±7.5	±7.0	±7.5	±6.0
Wt, kg	71.2	76.4	72.2	70.1	73.8	71.7
	±7.5	±8.8	±7.7	±10.0	±9.8	±8.1

Values are means ± SD; n, no. of subjects. * Includes 1 subject who did not complete the study.

determined. A few subjects were excluded at this point because of excessive heart rates (HR) associated with this level of exercise.

Each subject was randomly assigned to a single exposure at one of six O_3 concentrations: 0.0, 0.12, 0.18, 0.24, 0.30, or 0.40 ppm. The order of exposure was counterbalanced to control for possible day-of-the-week effects. Exposures were performed on Monday–Thursday mornings with either one subject alone or two subjects exposed together on any morning.

On the morning of exposure, subjects initially completed the symptom questionnaire and performed preexposure spirometry and plethysmography in clean air. They were then exposed to the appropriate O_3 concentration for 2.5 h. During the first 2 h of exposure, four cycles of 15 min rest and 15 min exercise were employed. Treadmill exercise was performed at the predetermined speed and grade of incline. Measurements of ventilation ($\dot{V}_E$, f, and V_T), oxygen consumption ($\dot{V}O_2$), and HR were obtained during the 11th and 12th min of each exercise period. In some cases (19%) the $\dot{V}_E$ was markedly different during the experiment from the approximately 35 l·min^{-1}·m^{-2} observed during training. The majority (84%) of these differences were obvious in the first period of exercise. Changes in exercise load were made for these subjects and also for subjects who developed excessively high HR. Spirometric and plethysmographic measurements were made 5 and 25 min, respectively, after the final exercise. Subjects again completed the symptom questionnaire 10 min after the final exercise. After exposure, the subject's health status was evaluated by a nurse and, if warranted, the subject was examined by a physician.

Spirometric measurements consisted of three forced vital capacity (FVC) maneuvers performed on a 12-liter dry-seal spirometer (CPI model 220). Graphic displays of each FVC manuever were evaluated, and those interrupted by cough were discarded. Expiratory volume in 1 s (FEV_1) and mean expiratory flow rate between 25 and 75% FVC (FEF_{25-75}) were also calculated for each FVC maneuver.

For each maneuver, FVC and FEV_1 were added and the mean FVC, FEV_1, and FEF_{25-75} from the two maneuvers with the highest sums were used. If only two satisfactory FVC maneuvers were obtained, means of the variables from both maneuvers were used, and if only one was obtained, the values from that maneuver were used.

Airway resistance (Raw), thoracic gas volume (Vtg), specific airway resistance (sRaw), and functional residual capacity (FRC) were determined according to the method of DuBois (6). Briefly, subjects were seated in a standard variable-pressure body plethysmograph (CPI model 2000TB) and panted at 1.5 Hz. Slopes of flow vs. box pressure were measured between −0.5 and +0.5 l/s flow, and 2–6 breaths were averaged for calculation of each variable. Measurements were made in triplicate, although in some instances less than three satisfactory measurements were obtained. Means of the variables from all satisfactory measurements were used.

During exercise, $\dot{V}_E$, tidal volume (V_T), and respiratory frequency (f) were obtained by digital integration of flow signals from a Fleisch no. 3 pneumotachometer. V_T and $\dot{V}_E$ were corrected to BTPS. Inspired and expired gases were continuously sampled at the mouth and analyzed by mass spectrometry (Perkin Elmer model MGA-1100). $\dot{V}O_2$ corrected to STPD, was calculated for each breath. Using single-channel telemetry, HR and electrocardiogram (ECG) were continuously monitored throughout exposure. $\dot{V}_E$, f, V_T, $\dot{V}O_2$, and HR were measured during the 11th and 12th min of exercise, and running averages were calculated every 10 s. The means of these running averages for the 12th min were used for analysis. Signals from the spirometer, plethysmograph, pneumotachometer, mass spectrometer, and ECG were analyzed in "real time" with a PDP 11/40 computer. All data were recorded on magnetic tape, and statistical analysis was performed at a later time.

The symptom questionnaires contained six questions regarding the presence and severity of cough, shortness of breath (SB), pain on deep inspiration (PDI), headache, eye itch, and sweating. The latter three were considered sham questions. Subjects were asked to classify their response to each question as none, mild, moderate, or severe. For purposes of statistical analysis, a score of 1 was assigned to none, 2 to mild, 3 to moderate, and 4 to severe.

Exposures and measurements were conducted in a 4 × 6 × 3.2-m stainless steel chamber maintained at 22°C and 40% relative humidity. O_3 was generated by passing incoming air over ultraviolet lights. The concentration of O_3 in the chamber was continuously monitored by chemiluminescence detection using Bendix model 8002 analyzers, which were periodically calibrated against an ultraviolet O_3 photometer (Dasibi model 1003AH). A detailed description of the chamber and the O_3-generating, delivery, monitoring, and control systems has been previously published (11, 25).

For pulmonary function variables and symptoms, differences between preexposure and final measurements were analyzed. For ventilatory control variables (V_T, f, $\dot{V}_E$) during exercise, differences between measurements obtained during the first and fourth exercise periods were analyzed. Data from subjects whose exercise intensity was changed during exposure were excluded from analysis of ventilatory control variables.

The nonparametric Williams procedure (23) was employed in the analysis of these data because, as indicated by Bartlett's test (30), the data did not meet the criterion of homogeneity of variance required for parametric sta-

tistical analysis. The Williams procedure is designed to compare several dose levels with a zero dose control and to determine the lowest dose at which there is evidence of a response. The procedure is restricted to analysis of data for which the means are either monotonically increasing or decreasing. Briefly the procedure consists of computing a two-sample t statistic (T-bar) for differences between the nonzero dose and the zero dose control and then comparing this statistic with a critical value that depends on the number of doses between the dose being tested and the zero control (28, 29).

Interpretation of statistically significant differences was influenced by the fact that nine variables were analyzed. When mutual independence of the variables measured is assumed, the probability of obtaining a P value less than 0.05 (the critical experiment-wide level of significance chosen for this study) for any one variable by chance alone increases as the number of variables analyzed increases. The most conservative way of accommodating this problem is by application of the Bonferroni inequality correction (4), which in this study entails the adjustment of the critical P value by dividing 0.05 by 9 (adjusted critical P value = 0.006). This correction is exact if the nine variables tested are mutually independent; otherwise it is conservative. In this study univariate correlation coefficients (r) among FVC, FEV_1, and FEF_{25-75} ranged between 0.67 and 0.91. Among the symptoms, r's ranged between 0.40 and 0.56 and the r between V_T and f was −0.71. Because the nine variables tested exhibited a significant degree of interdependence, the proper critical P value lies somewhere between 0.05 and 0.006, and we interpreted results from this study in this light. To aid the reader in evaluating our results, actual P values between 0.005 and 0.05 are reported.

An iterative least-squares method was used to fit four-parameter logistic function curves to mean changes of FVC, FEV_1, and sRaw at the six O_3 concentrations. The four parameters represent minimum and maximum response and the slope and location of the rapidly changing segment. For each curve, estimates of the logistic parameters and the proportion of the variance of the observed means accounted for by the fitted logistic function (R^2) were calculated.

TABLE 2. *Cardiopulmonary response to exercise*

	O_3, ppm					
	0.00	0.12	0.18	0.24	0.30	0.40
$\dot{V}_E$, l/min	66.2 ±7.6	68.0 ±7.4	64.6 ±6.9	64.9 ±7.6	65.4 ±7.6	64.3 ±7.1
$\dot{V}_E$/BSA, l·m^{-2}·min^{-1}	34.9 ±3.1	34.3 ±2.9	33.9 ±3.2	35.2 ±3.4	34.0 ±2.6	33.6 ±3.1
$\dot{V}o_2$, l/min	2.57 ±0.35	2.74 ±0.34	2.64 ±0.29	2.56 ±0.22	2.73 ±0.32	2.60 ±0.26
HR, beats/min	166 ±10	163 ±12	159 ±15	165 ±8	160 ±16	156 ±16

Values are means ± SD averaged over 4 exercise periods. $\dot{V}_E$, minute ventilation; BSA, body surface area; $\dot{V}o_2$, O_2 consumption; HR, heart rate.

RESULTS

$\dot{V}_E$, HR, and $\dot{V}o_2$ averaged over four exercise periods were similar for all exposure groups (Table 2). Mean treadmill speed was between 7.6 and 7.9 km/h and mean elevation between 11.3 and 12.1% grade for all groups.

Preexposure pulmonary function was within normal limits for all the subjects reported, and the means were similar for five of the six exposure groups (Table 3).

TABLE 3. *Initial and final measurements of pulmonary function during exposure to O_3*

	O_3, ppm					
	0.0	0.12	0.18	0.24	0.30	0.40
FVC, liters	(n = 20)	(n = 22)	(n = 20)	(n = 21)	(n = 20)	(n = 29)
I	5.34 ± 0.15	5.61 ± 0.16	5.49 ± 0.19	5.02 ± 0.17	5.38 ± 0.20	5.41 ± 0.15
F*	5.30 ± 0.14	5.44 ± 0.18	5.26 ± 0.17	4.49 ± 0.19	4.72 ± 0.22	4.77 ± 0.19
D	−0.05 ± 0.02	−0.17 ± 0.06	−0.23 ± 0.07	−0.53 ± 0.08	−0.66 ± 0.10	−0.64 ± 0.09
P		0.043	0.030	<0.005	<0.005	<0.005
FEV_1, liters						
I	4.42 ± 0.10	4.64 ± 0.12	4.50 ± 0.15	4.10 ± 0.11	4.41 ± 0.14	4.46 ± 0.12
F*	4.37 ± 0.09	4.44 ± 0.14	4.21 ± 0.13	3.51 ± 0.14	3.67 ± 0.17	3.70 ± 0.17
D	−0.05 ± 0.02	−0.21 ± 0.05	−0.29 ± 0.08	−0.59 ± 0.10	−0.74 ± 0.11	−0.76 ± 0.09
P		0.016	0.008	<0.005	<0.005	<0.005
FEF_{25-75}, l/s						
I	4.51 ± 0.22	4.87 ± 0.24	4.64‡ ± 0.29	4.11 ± 0.16	4.53 ± 0.22	4.60 ± 0.21
F*	4.49 ± 0.25	4.52 ± 0.23	4.09 ± 0.23	3.17 ± 0.15	3.44 ± 0.23	3.36 ± 0.22
D	−0.02 ± 0.07	−0.35 ± 0.11	−0.54 ± 0.18	−0.93 ± 0.17	−1.09 ± 0.23	−1.24 ± 0.14
P		0.03	0.009	<0.005	<0.005	<0.005
sRaw, cm/s	(n = 19)	(n = 22)	(n = 19)	(n = 21)	(n = 20)	(n = 28)
I	4.50 ± 0.33	4.34 ± 0.28	4.06 ± 0.35	3.87 ± 0.24	4.05 ± 0.34	4.11 ± 0.22
F†	4.43 ± 0.34	4.50 ± 0.27	4.29 ± 0.31	4.43 ± 0.28	4.90 ± 0.34	5.65 ± 0.36
D	−0.07 ± 0.09	0.16 ± 0.13	0.23 ± 0.12	0.56 ± 0.11	0.85 ± 0.23	1.54 ± 0.30
P		>0.05	>0.05	<0.005	<0.005	<0.005

Values are means ± SE; n, no. of subjects; FVC, forced vital capacity; FEV_1, forced expiratory volume in 1 s; FEF_{25-75}, mean expiratory flow rate between 25 and 75% FVC; sRaw, specific airway resistance; I, initial; F, final; D, difference. P values compare I-F differences of O_3-exposed groups with control group. * Final measurements made 5 min after 4th exercise period. † Final measurements made 25 min after 4th exercise period. ‡ n = 19.

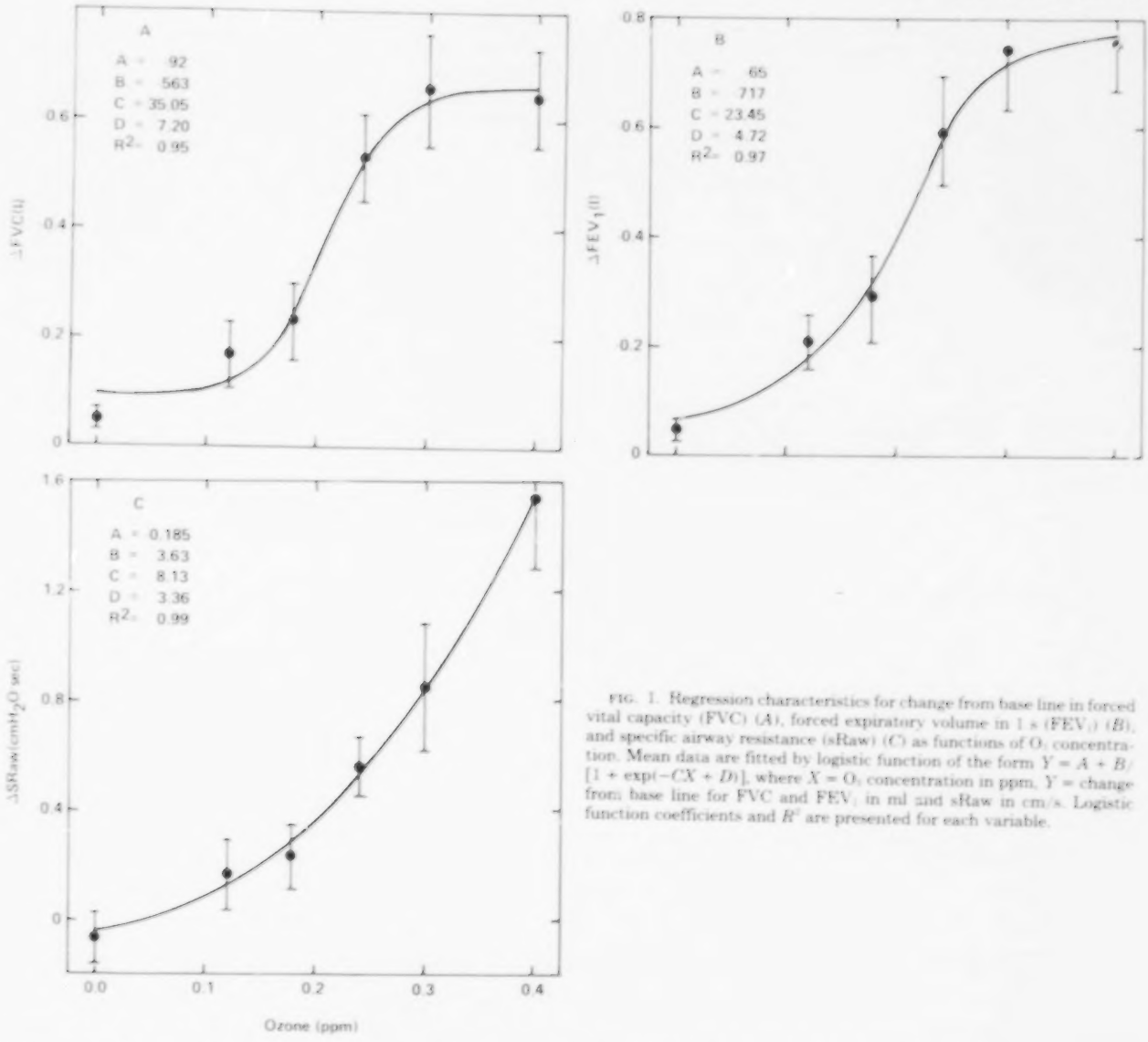

FIG. 1. Regression characteristics for change from base line in forced vital capacity (FVC) (*A*), forced expiratory volume in 1 s (FEV_1) (*B*), and specific airway resistance (sRaw) (*C*) as functions of O_3 concentration. Mean data are fitted by logistic function of the form $Y = A + B/[1 + \exp(-CX + D)]$, where X = O_3 concentration in ppm, Y = change from base line for FVC and FEV_1 in ml and sRaw in cm/s. Logistic function coefficients and R^2 are presented for each variable.

Spirometric flows and volumes were smaller in the 0.24-ppm O_3 group that was composed of shorter lighter men. Three subjects were excluded from statistical analysis. One subject who was exposed to 0.3 ppm O_3 did not complete the study due to development of severe symptoms, whereas two other subjects had preexposure values for FEV_1/FVC less than 65%.

Essentially no changes from preexposure were found for FVC, FEV_1, $FEF_{25-75\%}$, or sRaw after exposure of the control group to clean air (Table 3). Small group mean changes were measured in the three spirometric parameters at 0.12 (*P* values from 0.016 to 0.043) and 0.18 (*P* values from 0.008 to 0.030) ppm O_3, and larger changes were found at O_3 levels ≥ 0.24 ppm (all *P* values < 0.005). Significant changes in sRaw were found at O_3 levels ≥ 0.24 ppm (all *P* values < 0.005). These changes were entirely attributable to changes in Raw, because only small group mean changes from preexposure were found in Vtg (range −2.7 to +2.3%). Similarly changes in FRC were small (range −3.8 to +1.0%) and unrelated to O_3 dose.

Dose-response curves for group mean decrements in FVC and FEV_1 as functions of O_3 concentration (Fig. 1, *A* and *B*) are sigmoid shaped with a large increase occurring between 0.18 and 0.24 ppm O_3 and a plateau above 0.24 ppm O_3. Changes from base-line sRaw gradually increased with increasing O_3 concentration (Fig. 1*C*) without reaching a plateau at O_3 concentrations up to 0.40 ppm (the highest concentration tested).

The data for these variables were fitted by a logistic function of the form $Y = A + B/[1 + \exp(-CX + D)]$ where Y is the group mean change from base line, X is the O_3 concentration in ppm, and A–D are four estimated parameters for the model. Estimated parameters and R^2 for each variable are presented in Fig. 1.

The means of f, V_T (Table 4), and $\dot{V}_E$ (data not

TABLE 4. *Measurements of ventilatory control during exercise and exposure to O_3*

	O_3, ppm					
	0.0 (n = 17)	0.12 (n = 17)	0.18 (n = 19)	0.24 (n = 20)	0.30 (n = 13)	0.40 (n = 22)
f, min						
EX 1	30.8 ± 2.1	28.7 ± 1.5	30.3 ± 1.1	31.5 ± 1.5	28.2 ± 1.1	29.8 ± 1.3
EX 4	34.4 ± 2.2	33.0 ± 1.6	33.3 ± 1.6	39.9 ± 2.6	37.6 ± 2.7	42.4 ± 2.2
D	3.5 ± 1.5	4.3 ± 1.1	3.0 ± 1.1	8.4 ± 1.5	9.4 ± 2.2	12.6 ± 1.7
P		>0.05	>0.05	0.007	0.008	<0.005
VT, ml						
EX 1	2,213 ± 111	2,471 ± 136	2,157 ± 74	2,063 ± 111	2,405 ± 162	2,127 ± 88
EX 4	2,051 ± 118	2,132 ± 139	1,972 ± 69	1,616 ± 93	1,881 ± 127	1,594 ± 86
D	−162 ± 48	−339 ± 63	−185 ± 50	−447 ± 55	−524 ± 90	−533 ± 60
P		>0.05	>0.05	<0.005	<0.005	<0.005

Values are means ± SE; all measurements made 12 min into exercise period. f, Frequency; VT, tidal volume; EX 1, 1st exercise period; EX 4, 4th exercise period; D, difference. *P* values compare EX 1–EX 4 differences of O_3-exposed groups with control group.

TABLE 5. *Symptom measurements before and after exposure to O_3*

	O_3, ppm					
	0.0	0.12	0.18	0.24	0.30	0.40
	(n = 17)	(n = 21)	(n = 19)	(n = 20)	(n = 18)	(n = 28)
Cough						
I	1.1 ± 0.1	1.0 ± 0.0	1.0 ± 0.0	1.2 ± 0.1	1.1 ± 0.1	1.1 ± 0.0
F*	1.1 ± 0.1	1.8 ± 0.2	1.8 ± 0.2	2.4 ± 0.2	2.6 ± 2.2	2.4 ± 0.1
D	0.1 ± 0.1	0.8 ± 0.2	0.8 ± 0.1	1.3 ± 0.2	1.6 ± 0.2	1.4 ± 0.1
P		<0.005	<0.005	<0.005	<0.005	<0.005
	(n = 15)	(n = 20)	(n = 19)	(n = 19)	(n = 19)	(n = 27)
PDI						
I	1.0 ± 0.0	1.0 ± 0.0	1.0 ± 0.0	1.0 ± 0.0	1.0 ± 0.0	1.0 ± 0.0
F*	1.4 ± 0.1	1.6 ± 0.2	1.7 ± 0.2	2.2 ± 0.2	2.4 ± 0.2	2.5 ± 0.2
D	0.4 ± 0.1	0.6 ± 0.2	0.7 ± 0.2	1.2 ± 0.2	1.4 ± 0.2	1.5 ± 0.2
P		>0.05	>0.05	0.008	<0.005	<0.005
	(n = 17)	(n = 21)	(n = 20)	(n = 20)	(n = 17)	(n = 28)
SB						
I	1.1 ± 0.1	1.0 ± 0.0	1.0 ± 0.0	1.0 ± 0.0	1.0 ± 0.0	1.0 ± 0.0
F*	1.5 ± 0.1	1.8 ± 0.1	1.9 ± 0.1	2.5 ± 0.2	2.5 ± 0.2	2.5 ± 0.1
D	0.5 ± 0.1	0.8 ± 0.1	0.9 ± 0.1	1.4 ± 0.2	1.5 ± 0.2	1.5 ± 0.1
P		>0.05	>0.05	<0.005	<0.005	<0.005

Values are means ± SE; *n*, no. of subjects; PDI, pain upon deep inspiration; SB, shortness of breath; I, initial; F, final; D, difference. *P* values compare I-F differences of O_3-exposed groups with control group. * Final measurements made 10 min after 4th exercise period. Presence and severity of symptoms measured 1 as none, 2 as mild, 3 as moderate, and 4 as severe.

presented) were similar for all six groups during the first period of exercise. Clean air exposure was associated with a mean increase of 11.7% in f and a mean decrease of 7.3% in VT between exercise periods one and four. Similar changes were found for exposure to 0.12 and 0.18 ppm O_3 (P value > 0.05). Larger changes in f and VT were observed at levels of $O_3 \geq 0.24$ ppm (P value < 0.005–0.008). The shape of the dose-response relationships for these variables is similar to that observed for FVC and FEV_1. No exposure group exhibited changes in VE significantly different from that seen in the control group.

Few symptoms were reported in any group before exposure (Table 5). After exposure to clean air, no increase in cough was observed. Small increases in cough were noted at 0.12 and 0.18 ppm (P values < 0.005), whereas larger increases occurred at O_3 levels ≥ 0.24 ppm (P values < 0.005). Small increases in SB and PDI were present after exposure to clean air and to 0.12 and 0.18 ppm O_3 (P values > 0.05), whereas larger increases were found at O_3 levels ≥ 0.24 ppm (P values < 0.005). The severity of symptoms stabilized at O_3 levels ≥ 0.24 ppm. Changes for each of the three sham symptoms during all O_3 exposures were similar to those during clean air exposure.

In addition to group mean changes, changes from preexposure FEV_1 and sRaw for individual subjects were assessed. Minimal variability in response among individuals was found for sRaw and FEV_1 after clean air exposure (Fig. 2). However, as the levels of O_3 increased, a wide range of individual responses to O_3 occurred. Individual variability appears to increase for FEV_1 at O_3 levels ≥ 0.24 ppm and for sRaw at O_3 levels ≥ 0.3 ppm. Individuals manifesting large changes in spirometric variables did not necessarily have large changes in sRaw. The correlation coefficients for individual changes of FEV_1 and FVC relative to changes in sRaw were low (−0.31 and −0.16, respectively) for the five groups exposed to O_3.

DISCUSSION

Acute changes in pulmonary function and development of symptoms during exposure at rest to O_3 levels > 0.5

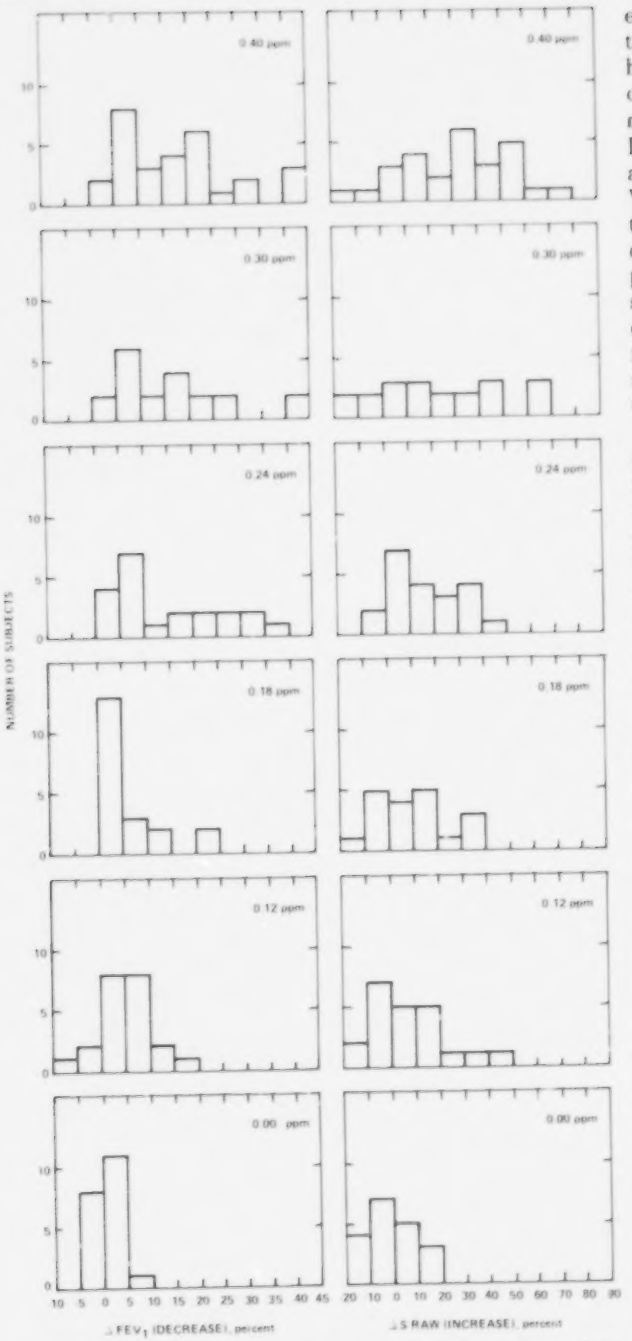

FIG. 2. Frequency distributions of response (percent change from base line) in specific airway resistance (sRaw) and forced expiratory volume in 1 s (FEV_1) for individuals exposed to 6 levels of O_3. One individual with 260% increase in sRaw exposed to 0.4 ppm O_3 is not graphed.

ppm have been documented (3, 9, 24, 31). Exercise during exposure increases the magnitude of pulmonary function changes at a given level of O_3 and decreases the concentration of O_3 necessary to induce such changes (3, 7, 9). This observation led to the development of the concept of "effective" dose of O_3 that was calculated by Silverman et al. (24) to be a function of the product of O_3 concentration and $\dot{V}_E$. Adams et al. (1) and Folinsbee et al. (7) have demonstrated that at O_3 levels $\geq$ 0.3 ppm, O_3 concentration is more important in determining pulmonary function changes than is $\dot{V}_E$ or duration of exposure. Folinsbee et al. (7) modified the effective dose concept, and, by appropriately weighting O_3 concentration and $\dot{V}_E$, have developed equations for predicting the magnitude of changes in spirometric parameters. Because no data from exposures to levels of O_3 between 0.11 and 0.27 ppm were included in formulating these equations, considerable uncertainty exists about the characteristics of dose-response curves in this region. To better assess this relationship, we held $\dot{V}_E$ and duration of exposure constant and exposed subjects to three levels of O_3 (0.12, 0.18, and 0.24 ppm) between 0.1 and 0.27 ppm.

A primary purpose of this study was to discern the lowest concentration of O_3 at which group mean decrements in pulmonary function occur. In this study, decrements, as measured by spirometry, were clearly demonstrated for exposure to 0.18 ppm O_3 and were suggested for exposure to 0.12 ppm O_3. These results are somewhat different from those of previous studies in which exercise of similar duration and ventilation was employed and the alterations in pulmonary function at low O_3 concentrations were judged to be nonsignificant (1, 5, 7). In the study of Folinsbee et al. (7), subjects were exposed to 0.11 ppm O_3. Although not statistically significant, small decreases in mean FVC and FEV_1 (1.9 and 2.6%, respectively) were observed. In the DeLucia and Adams study (5) the actual group mean data were not presented for the 0.15-ppm O_3 exposure, but, of the four subjects for whom individual data were presented, three had decrements in FEV_1 from 8 to 10%. Small sample size ($n = 6$) and individual variability in response may have limited their ability to assess the significance of small changes. Small sample size ($n = 8$) may have also been a factor in the study of exposure to 0.20 ppm O_3 by Adams et al. (1).

To facilitate prediction of group mean response for FVC, FEV_1, and sRaw at intermediate levels of O_3, the mean data for six exposure groups were fitted by the four-parameter logistic function that describes a sigmoid curve. The fits of the observed means were excellent, as evidenced by the high correlation coefficients (Fig. 1). The configuration of the dose-response curve for sRaw, as well as the magnitudes of change at individual O_3 levels, is consistent with the results of Folinsbee et al. (7). The sigmoid-shaped dose-response curves for spirometric variables, with large decreases in FVC and FEV_1 between 0.18 and 0.24 ppm O_3 and a plateau at higher levels (> 0.24 ppm) of O_3, however, was unexpected, because Folinsbee et al. (7) had not observed such a plateau between 0.27 and 0.43 ppm O_3. The most likely explanation for this discrepancy is chance selection in either study of a sample of individuals not representative of the underlying population. Assuming that this plateau in response is valid for the population, these results are consistent with some step in the pathway of reduction of FVC reaching a level of stimulation beyond which further stimulation of < 0.40 ppm O_3 produces no further change in response. In contrast, there is no evidence that response to O_3, as measured by changes in sRaw, reaches a plateau at O_3 levels < 0.40 ppm. This difference in

response, coupled with the observation that there is no correlation between changes in sRaw and FVC ($r = -0.16$) for individual subjects, suggests that O_3 may have effects mediated by more than one mechanism.

Decrements in FVC at 0.3 and 0.5 ppm O_3 have been attributed to changes in total lung capacity (TLC) without significant changes in residual volume (7, 8, 13), although exposure to 0.75 ppm O_3 may be associated with increases in residual volume (15, 24). Changes in TLC after exposure to $O_3 < 0.5$ ppm are thought to represent a decrease in inspiratory effort rather than a decrease in lung compliance (3, 7, 17, 24). It is currently speculated that this decreased effort results from "sensitization" or stimulation of irritant (rapidly adapting) and possibly other airway receptors (7, 12, 16, 18, 19), resulting in inhibition of maximal inspiration, either involuntarily or due to discomfort (1, 3).

Possible mechanisms of airway narrowing include smooth muscle contraction, mucosal edema, or secretion of mucus resulting from vagally mediated reflexes from irritant receptor stimulation (21, 22, 27), interaction of an endogenous or exogenous substance with the vagal efferent pathway (14, 20), or direct action of O_3 or an O_3-related locally released substance on smooth muscle or mucosa. Increases in sRaw as a result of O_3 exposure are thought to be due to airway narrowing through one or more of the above mechanisms (7, 16, 26). Though O_3-induced sensitization of airway receptors resulting in changes in both FVC and sRaw is an attractive hypothesis, the difference in patterns of response for these two variables imposes constraints on the degree of overlap of the mechanisms responsible for these changes. If stimulation of a single class of airway receptor is active in both mechanisms, then some further interaction of O_3 with one or both response pathways is necessary to account for the lack of correlation between changes in FVC and sRaw and the differences in dose-response curves.

Decrements in maximal expiratory flows, unless measured at absolute volumes, are difficult to interpret. In this case the measured decrements are probably partially accounted for by reductions in maximal inspiratory position. Further decrements may be the result of airway narrowing. This view is supported by the high correlation of changes in FEV_1 and FEF_{25-75} with changes in FVC and by the small rate of decrease in FEV_1 and FEF_{25-75} at > 0.24 ppm O_3 associated with a stable FVC and increasing sRaw.

Our findings of significantly increased f and decreased V_T during exercise at O_3 levels ≥ 0.24 ppm in the absence of significant changes in $\dot{V}_E$, are in agreement with results from other studies (1, 5, 9). In dogs, similar changes observed during exposure to O_3 were abolished by vagal cooling, implicating vagal afferent pathways probably stimulated by airway receptors (19). The altered ventilatory control we observed was first evident at the same level of O_3 at which major changes in spirometric variables occurred and exhibited a similar plateau at higher O_3 levels. This observation is consistent with the concept that O_3-induced stimulation or sensitization of airway receptors is a component common to the mechanisms underlying both the decrease in FVC and changes in f and V_T.

The symptoms observed in this study correspond to symptoms reported elsewhere (13, 15, 17). For each exposure group, we developed a measure incorporating both severity of symptom and number of individuals affected. Of all symptoms measured, cough proved most sensitive to O_3 exposure. This probably reflects stimulation of airway irritant receptors. For all symptoms, the general shapes of dose-response curves were similar to those of spirometric and respiratory control variables.

We have focused on group mean changes induced by O_3 exposure, because this approach permits population inferences to be made. Because a large range of individual response was observed, especially at higher levels of O_3 (Fig. 2), it is important to examine individual responses in addition to the mean response. The abrupt increase in range of individual response at O_3 levels ≥ 0.24 ppm, and the steep slope of the dose-response curve between 0.18 and 0.24 ppm O_3 for mean changes in FVC, FEV_1, and FEF_{25-75} (Fig. 1), suggest that the majority of individuals in this population who perform heavy exercise will first manifest O_3-induced changes in FVC in the relatively narrow interval between 0.18 and 0.24 ppm O_3 but will have a large range of maximal response. Further studies of individual dose-response relationships would be necessary to test this hypothesis. Factors responsible for the large range in maximal response have not been elucidated.

In summary, we have exposed heavily exercising healthy men to low levels of O_3 and have observed a definite increase in cough and the suggestion of spirometric decrements at 0.12 ppm. Definite changes in some variables were present at 0.18 ppm and in all variables that were measured at O_3 levels ≥ 0.24 ppm. Our results are consistent with the hypothesis that many of these responses result from stimulation or sensitization of airway receptors by O_3, but a second mechanism of action is postulated to explain differences in response between sRaw and FVC. Large differences in individual response were observed and are unexplained.

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